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(54) **Coating membrane and compositions prepared therefrom.**

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EP 0 263 083 B1

Description

This invention relates to a coating membrane for pharmaceutical and industrial purposes and to compositions prepared therefrom. More particularly it relates to a coating membrane for the controlled release of an active ingredient which may be of pharmaceutical, veterinary, synthetic or extractive type, and to compositions containing said coated active ingredient.

In the pharmaceutical field, the production of sustained release microgranules is known (see for example EP 123,470 and 122,077).

The preparation involves the application of the active ingredient on a spherical nucleus having a diameter of from 0.2 to 2 mm by means of a particular binding agent, or a spherical nucleus of active ingredient with or without binding agent may bre prepared. Then a semi-permeable membrane is applied, which allows the diffusion of the drug over a controlled period of time or it disgregates over a well-established period of time releasing the drug.

The membrane normally used and described in several patents consists of: shellac, methacrylic acid copolymers, ethylcellulose, ethylcellulose phtalate, hydroxypropyl methylcellulose, cellulose acetophtalate, etc. The abovementioned and currently used membranes are also of natural source, such as shellac, and thus of indefinite composition. As a consequence, the amounts used to obtain an identical coating notably change from time to time and give, therefore, stability problems. The productions from batch to batch are thus difficult, and often it is not possible to obtain the same release pattern.

Moreover, it is very difficult to reach a zero order release or a release over a controlled period of time according to the drug needs.

In the pharmaceutical field, the purpose of the sustained release formulations is to obtain a 12 hours therapeutically active hematic level with consequent posology of two daily administrations, or a 24 hours hematic level with administration of a sole capsule a day. In order to achieve said results, the drug release has to be more or less delayed according to the characteristic half-life of each drug.

In FR-A-2 237 620 a pharmaceutical oral controlled release composition is described containing spherical particles of a medicament provided with a dialysis membrane, wherein the film-forming agent of said membrane comprises from 15 to 70% by weight of a component "a" and from 85 to 30% by weight of a component "b", said "a" being a cellulose ether insoluble at the pH value of the gastro-intestinal tract, not decomposable by enzymes present in said tract, and which has an alcoxy groups content of from 43 to 50% by weight and a viscosity of 7-100 centipoises, and "b" is selected from several organic compounds essentially soluble in the intestinal tract only, the free carboxylic groups content of said "b" being of from 5 to 40% by weight.

It has now been found that, modifying the amount of the applied membrane or the ratios between two components, it is possible to obtain sustained releases from 4-6 hours up to 18-22 hours and higher, as shown in figure 1 for ketoprofen (ethylcellulose/stearic acid membrane) and in figure 2 for diltiazem hydrochloride (paraffin/methacrylic acid copolymers membrane).

This technological flexibility allows to choose the most suitable in vitro release for obtaining the in vivo blood level which provides the pharmaceutical effect over a desired period of time.

Several tests have shown a very good reproducibility from batch to batch and good stability. Membranes from synthetic products with a well-definite molecular composition, and often reported in International Pharmacopeias, provide an improved purity, as shown by the analytical tests.

These new membranes, like paraffin, have for their own nature a very low chemical affinity for the products which have to be coated. In this way, a very good compatibility does exhist between membrane and product to be coated, and a good time stability may be achieved.

Accordingly, the present invention relates to the use, as semipermeable or breakable membranes, of certain lipophilic compounds alone or in admixture with a suitable hardening agent. More particularly the present invention relates to a coating membrane for pharmaceutical, cosmetic, veterinary, synthetic and extractive substances and to the compositions prepared therefrom. The composition of the invention is defined in claim 1. Preferred embodiments thereof are set forth in claims 2-8.

In a further embodiment, the invention provides also a method for preparing said compositions, which comprises coating inert material pellets with a first layer of a therapeutically active compound and applying then thereon a second layer consisting of a particular lipophilic substance, alone or in admixture with a particular hardening agent.

In the compositions of the present invention, the inert pellets comprise preferably sucrose and starch.

The particular substances used as lipophilic membranes are the following:

A) Fatty acids containing from 12 to 20 carbon atoms, such as palmitic acid, stearic acid and/or paraffin (USP XXI, page 1584).

The compounds utilized for having hardening action are selected from :

B) Ethylcellulose Hercules*with Ethoxy groups 44.5 to 50%.

C) Methacrylic acid copolymers (Rohm Pharma GmbH) Eudragit*E, L, S, RS, RL, E 30D, L 30D, RL 30D, RS 30D type.

The hardening agents mentioned above are preferably dissolved in ethanol, acetone, methylene chloride or in other organic solvents at room temperature or at a temperature corresponding to the boiling point of the employed solvent. In this way, 0.1% to saturated solutions may be obtained. The hardeners can be dissolved alone or mixed each other in all the proportions.

The lipophilic substances are dissolved in the above solvents or they are melted. They can be used alone or in admixture each other, and they are applied meted or in solution.

Tests carried out on theophylline with stearic acid alone as membrane, show a faster release in comparison with that obtained with the same amount of stearic acid but added with hydroxypropylmethylcellulose. Adding hardening agents to the lipophilic compounds, a more flexible and less rapid realese over a controlled period of time may be achieved. In order to obtain mechanically harder and more stable membranes, the lipophilic compounds should be blended with the hardening agents in solution, where possible, or in alternate layers.

The application of the membranes on microgranules or other material which has to be coated, is done for achieving: a slow release of the coated material, gastroprotection, separation of incompatible substances, reduction of the chemical reactivity, physical separation, handling improvement, to eliminate bad smell and taste, stability improvement. The melted or solubilized membrane is applied on the material which has to be coated by means of high pressure pump in order to subdivide it in microdrops.

Said procedure is carried out in stainless steel coating pans with variable rotation speed from 3 to 40 rpm according to the diameter, with a fluid bed apparatus (uni-glatt) or in fast mixers, such as Loeding type or the like. The evaporation of the solvents utilized in the process, is performed in thermostatic dryers or under vacuum at a temperature of from 30 ° to 45 ° C.

The lipophilic compounds, alone or mixed each other, and with possible addition of hardening agents, can also be used with spray dry or spray cooling techniques.

The following examples illustrate the invention and facilitate its understanding.

Example 1

On 19 kg of neutral pellets, consisting of 75% w/w of sucrose and 25% (w/w) of starch and placed in a stainless steel coating pan, ketoprofen was applied (53.5 kg) with a 20% (w/w) alcoholic solution (ethanol) of polyethylene glycol (MW 4000). After drying, a 4.5% (w/w) alcoholic solution of ethylcellulose (with 44.5 to 50% of ethoxy groups) and 7.5% of stearic acid was applied, with addition of 2.70 kg of talc.

After drying, the product contained 2.23 kg (4.16% by weight based on the medicament mass) of stearic acid (NF XVI, page 1611) and 1.33 kg (2.48% by weight based on the medicament mass) of ethylcellulose. The release test, carried out according to USP XXI Apparatus No. 1, at 150 rpm and with 900 ml of juice of pH 7.2, provided the results reported in figure 1, curve D. The curves A to C were obtained with formulations having increased amounts or membrane. With said formulation, capsules containing from 50 to 250 mg of ketoprofen may be prepared.

Example 2

82.00 kg of paracetamol were placed in a Loedige type mixer, and under stirring 12.40 kg (15.12% by weight based on the medicament mass) of stearic acid (NF XVI, page 1611), melted and blended with 25.00 kg of a 10% (w/w) ethanolic solution of ethylcellulose (44.5-50% ethoxy groups), were added at a temperature of 50-60 ° C (3.05% by weight of the ethylcellulose based on the medicament mass).

The mass was stirred for 10-15 minutes and then dried in a thermostatic box at 35-45 ° C. The granulate thus obtained had a masked taste and can be used in monodose bags or in other pharmaceutical forms. The granulate was mixed with 3.00 kg of magnesium stearate and tablets containing from 200 mg to 1 g of paracetamol were then prepared.

The release test, accomplished according to USP XXI, Apparatus No. 2, at 50 rpm and with 900 ml of juice of pH 5.8, showed the following release results:

1st hour = 22.8%

4th hour = 54.6%

* Trade Name

8th hour = 98.3%.

The release rate was increased or decreased by proportionally varying the amount of the applied membrane.

It should be noted that instead of a Loedige type mixer, a fluid bed or stainless steel coating pan may be used and with the same membrane comparative results may be obtained.

Example 3

Operating as described in Example 2, but applying only 10% of membrane (corresponding to 1.512% by weight of stearic acid and 0.305% by weight of ethylcellulose, based on the medicament mass), tablets were obtained showing a very rapid release. With a further coating of the tablets in the stainless steel pan using from 10 to 20% of the same membrane, the following release profile was obtained:

1st hour = 10-25%

4th hour = 40-80%

8th hour = 70-100%.

Example 4

Operating as described in Example 1, on 34.40 kg of inert granules (size 0.7 - 1 mm) 49.50 kg of propanolol HCl were applied with 11.00 kg of a 20% (w/w) ethanolic solution of polyvinylpyrrolidone (k value = 30).

The membranes were applied in successive layers for a total weight of 8.10 kg (16.35% by weight based on the medicament mass) of paraffin previously melted and diluted to a 40% concentration with methylene chloride at a temperature of 30-45 ° C.

The methacrylic acid copolymers (Rohm Pharma, Eudragit E*and RS type) were applied in acetonic solution (1.81% by weight based on the medicament mass). The end amounts were as follows:

Eudragit RS*kg 0.60; Eudragit E*kg 0.30.

During the application of the successive layers 4.80 kg of talc were added.

The release test, carried out according to USP XXI, Apparatus No. 1, at 100 rpm and with 900 ml of juice or pH 1.2 for the first hour and of 7.5 for the fourth and eighth hour, gave the following results:

1st hour = 13.3%; 4th hour = 47.2%; 8th hour = 82.8%.

After administration of a capsule containing 160 mg of propranolol HCl, the in vivo results showed a pharmacologically active blood level for 24 hours as the known product Inderal LA*available in Switzerland,England, etc. With the above formulation, capsules containing from 40 to 250 mg of propranolol HCl may be prepared.

Example 5

Operating as described in Example 4 but with the following per cent composition on dried microgranules

* Trade Name

* Trade name

diltiazem HCl	43.6%
neutral granules	22.5% (size 0.7-1 mm)
paraffin (USP XXI, page 1584)	13.0% (28.8% of the medicament mass)
Polyvinylpyrrolidone (USP XXI, page 1584)	8.8%
Eudragit E® (Rohm Pharma)	2.1% (6.65% of the medicament mass)
Eudragit RS® (Rohm Pharma)	0.8%
talc	9.2%

(® Trade name)

the analysis, performed according to USP XXI, Apparatus No. 1, at 100 rpm and in 800 ml of HCl N/10, provided the results reported in Table 2, curve D. The other curves were obtained by increasing or decreasing the membrane amount in comparison with that indicated above. These different release rates were guaranted by a very good reproducibility.
With the above indicated formulation, capsules containing from 50 to 250 mg of diltiazem can be obtained.

Example 6

69.30 kg of neutral microgranules (granular size 0.9 - 1.1 mm) were placed in a stainless steel pan and 23.00 kg of isosorbide-5-mononitrate were applied after dissolution in 20.00 kg of acetone and 45.00 kg of methylene chloride in which 0.95 kg of ethylcellulose (ethoxy groups 44.5 - 50%) were dissolved.

After drying, the membrane was applied from ethanolic solution. The dried microgranules contained 6.05 kg (26.3% by weight based on the medicament mass) of ethylcellulose, 0.655 kg (2.84% by weight based on the medicament mass) of stearic acid (NF XVI, page 1611) and 85 g of talc.
The analysis according to USP XXI, Apparatus No. 2, at 100 rpm and with 1000 ml of juice of pH 7.5, provided the following release results:
1st hour = 29.7%
4th hour = 70.4%
8th hour = 88.7%.

The studies on 8 volunteers with 50 mg capsules, in comparison with the known product Elantan*Long, available in Germany, showed a very good bioequivalence with a posology of one daily capsule.

With the above formulation, capsules containing from 20 to 120 mg of isosorbide-5-mononitrate may be prepared.

Example 7

Operating as described in Example 6, but with the following per cent composition:

phenylpropanolamine HCl	31.6%
neutral granules	56.5% (0.7-1 mm)
polyvinylpyrrolidone	2.0% (k value = 30)
ethylcellulose	7.7% (ethoxy groups 44.5-50%) (24.3% by weight based on the medicament mass)
stearic acid (NF XVI, page 1611)	0.7% (2.43% by weight based on the medicament mass)
talc	1.5%

* Trade Name

the analysis according to USP XXI, Apparatus No. 1, at 100 rpm, with 500 ml of distilled water, gave the following results:
1st hour = 51.8%
2nd hour = 72.2%
4th hour = 96.4%
The per cent release was the same as for the known product Dexatrin*, available in Switzerland and U.S.A. - With the above described formulation capsules containing from 10 to 150 mg may be prepared.

Example 8

On 33.00 kg of neutral microgranules, prepared as described in Example 1, 40.00 kg of diacerheyn were applied using a binding agent comprising a solution containing 10.20 kg of polyethylene glycol 4000 and 40.00 kg of ethanol.
After drying, a membrane comprising 42.20 kg of ethanol, 2.20 kg (5.5% by weight based on the medicament mass) of ethylcellulose (ethoxy groups 44.5 - 50.0%) and 0.500 kg (1.25% by weight based on the medicament mass) of stearic acid was applied in solution.
The test was performed according to USP XXI, Apparatus No. 2, at 100 rpm, with 900 ml of juice of pH 7.5 added with 0.05% (w/w) of Tween*80, and it gave the following results:
1st hour = 47%
4th hour = 73%
8th hour = 88%
12th hour = 94%.

Claims

1. A pharmaceutical oral controlled release composition comprising a multiplicity of small pellets consisting of microgranules of inert material, a medicament layer applied thereon and a coating membrane applied upon the medicament layer, said coating membrane being a mixture of stearic acid and ethylcellulose or of paraffin and methacrylic acid copolymers, characterized in that the medicament is selected from the group consisting of ketoprofen, paracetamol, propanol, diltiazem, isosorbide-5-mononitrate, phenylpropanolamine and diacerheyn, wherein, when the medicament is selected from the group consisting of ketoprofen, paracetamol, phenylpropanolamine, isosorbide-5-mononitrate and diacerheyn, the coating membrane comprises a mixture of stearic acid and ethylcellulose, and when the medicament is selected from the group consisting of propranolol and diltiazem, the coating membrane comprises a mixture of paraffin and methacrylic acid copolymer, and in that the medicament sustained release in vitro achieved is of from 4 to 22 hours or longer.

2. A pharmaceutical composition according to claim 1, characterized in that the medicament is ketoprofen and the coating membrane comprises 4.16% by weight of stearic acid and 2.48% by weight of ethylcellulose, based on the mass of the medicament.

3. A pharmaceutical composition according to claim 1, characterized in that the medicament is paracetamol and the coating membrane comprises 15.12% by weight of stearic acid and 3.05% by weight of ethylcellulose, based on the mass of the medicament.

4. A pharmaceutical composition according to claim 1, characterized in that the medicament is isosorbide-5-mononitrate and the coating membrane comprises 2.84% by weight of stearic acid and 26.3% by weight of ethylcelulose, based on the mass of the medicament.

5. A pharmaceutical composition according to claim 1, characterized in that the medicament is phenylpropanolamine and the coating membrane comprises 2.43% by weight of stearic acid and 24.3% by weight of ethylcellulose, based on the mass of the medicament.

6. A pharmaceutical composition according to claim 1, characterized in that the medicament is diacerheyn and the coating membrane comprises 1.25% by weight of stearic acid and 5.5% by weight of ethylcellulose, based on the mass of the medicament.

* Trade Name

7. A pharmaceutical composition according to claim 1, characterized in that the medicament is propranolol and the coating membrane comprises 16.36% by weight of paraffin and 1.81% by weight of methacrylic acid copolymer, based on the mass of the medicament.

8. A pharmaceutical composition according to claim 1, characterized in that the medicament is diltiazem and the coating membrane comprises 29.8% by weight of paraffin and 6.65% by weight of methacrylic acid copolymer, based on the mass of the medicament.

9. A process for preparing a pharmaceutical oral controlled release composition according to claim 1, comprising coating microgranules of inert material with a medicament layer and applying a coating membrane upon said medicament layer, characterized in that the medicament is selected from the group of ketoprofen, paracetamol, propranolol, diltiazem, isosorbide-5-mononitrate, phenylpropanolamine and diacerheyn and the coating membrane is a mixture of stearic acid and ethylcellulose or of paraffin and methacrylic acid copolymers, wherein, when the medicament is selected from the group consisting of ketoprofen, paracetamol, phenylpropanolamine, isosorbide-5-mononitrate and diacerheyn, the coating membrane comprises a mixture of stearic acid and ethylcellulose, and when the medicament is selected from the group consisting of propranolol and diltiazem, the coating membrane comprises a mixture of paraffin and methacrylic acid copolymer.

10. The process according to claim 9, characterized in that the coating membrane is applied from a solution containing both the components stearic acid/ethylcellulose or paraffin/methacrylic acid copolymer.

11. The process according to claim 9, characterized in that the coating membrane is applied in alternate and separate layers while in a melted state.

Patentansprüche

1. Pharmazeutische, mündlich freiwerdende Komposition, enthaltend eine Anzahl von kleinen Pellets in Form von Mikrogranulat aus trägem Material, eine auf diese aufgetragene Medikamentenschicht und ein Überzugsmembran, das über der Medikamentenschicht angebracht ist, wobei das genannte Überzugsmembran aus einer Mischung aus Stearinsäure und Äthylzellulose oder aus Paraffin und Methcrylsäure-Kopolymeren besteht, **dadurch gekennzeichnet,** dass das Medikament aus der aus Ketoprofen, Paracetamol, Propranolol, Diltiazem, Isosorbid-5-Mononitrat, Phenylpropanolamin und Diazerheyn bestehenden Gruppe gewählt ist, wobei, wenn das Medikament aus der aus Ketoprofen, Paracetamol, Phenylpropanolamin, Isosorbid-5-Mononitrat und Diacerheyn bestehenden Gruppe gewählt ist, das Überzugsmembran eine Mischung aus Stearinsäure und Äthylzellulose enthält, und wenn das Medikament aus der aus Propranolol und Diltiazem bestehenden Gruppe gewählt ist, das Überzugsmembran eine Mischung aus Paraffin und Methacrylsäure-Kopolymer enthält, und **dadurch,** dass die erreichte ungedämpfte Medikamentenfreigabe in Vitro von 4 bis 22 Stunden oder länger ist.

2. Pharmazeutische Komposition nach Patentanspruch 1, **dadurch gekennzeichnet,** dass das Medikament aus Ketoprofen besteht und das Überzugsmembran 4,16% des Gewichtes an Stearinsäure und 2,48% des Gewichtes an Äthylzellulose enthält, basierend auf der Masse des Medikamentes.

3. Pharmazeutische Komposition nach Patentanspruch 1, **dadurch gekennzeichnet,** dass das Medikament aus Paracetamol besteht und das Überzugsmembran 15,12% des Gewichtes an Stearinsäure und 3,05% des Gewichtes an Äthylzellulose enthält, basierend auf der Masse des Medikamentes.

4. Pharmazeutische Komposition nach Patentanspruch 1, **dadurch gekennzeichnet,** dass das Medikament aus Isosorbid-5-Mononitrat besteht und das Überzugsmembran 2,84% des Gewichtes an Stearinsäure und 26,3% des Gewichtes an Äthylzellulose enthält, basierend auf der Masse des Medikamentes

5. Pharmazeutische Komposition nach Patentanspruch 1, **dadurch gekennzeichnet,** dass das Medikament aus Phenylpropanolamin besteht und das Überzugsmembran 2,43% des Gewichtes an Stearinsäure und 24,3% des Gewichtes an Äthylzellulose enthält, basierend auf der Masse des Medikamentes.

6. Pharmazeutische Komposition nach Patentanspruch 1, **dadurch gekennzeichnet,** dass das Medikament aus Diacerheyn besteht und das Überzugsmembran 1,25% des Gewichtes an Stearinsäure und 5,5% des Gewichtes an Äthylzellulose enthält, basierend auf der Masse des Medikamentes.

7. Pharmazeutische Komposition nach Patentanspruch 1, **dadurch gekennzeichnet,** dass das Medikament aus Propranolol besteht und das Überzugsmembran 16,36% des Gewichtes an Paraffin und 1,81% des Gewichtes an Methacrylsäure-Kopolymer enthält, basierend auf der Masse des Medikamentes.

8. Pharmazeutische Komposition nach Patentanspruch 1, **dadurch gekennzeichnet,** dass das Medikament aus Diltiazem besteht und das Überzugsmembran 29,8% des Gewichtes an Paraffin und 6,65% des Gewichtes an Methacrylsäure-Kopolymer enthält, basierend auf der Masse des Medikamentes.

9. Verfahren zur Herstellung einer pharmazeutischen, mündlich freiwerdenden Komposition nach Patentanspruch 1, welches das Überziehen von Mikrogranulat aus trägem Material mit einer Medikamentenschicht vorsieht sowie das Anbringen eines Überzugsmembrans über der genannten Medikamentenschicht, **dadurch gekennzeichnet,** dass das Medikament aus der aus Ketoprofen, Paracetamol, Propranolol, Diltiazem, Isosorbid-5-Mononitrat, Phenylpropanolamin und Diazerheyn bestehenden Gruppe gewählt und das Überzugsmembran eine Mischung aus Stearinsäure und Äthylzellulose oder aus Paraffin und Methacrylsäure-Kopolymer ist, wobei, wenn das Medikament aus der aus Ketoprofen, Paracetamol, Phenylpropanolamin, Isosorbid-5-Mononitrat und Diacerheyn bestehenden Gruppe gewählt ist, das Überzugsmembran eine Mischung aus Stearinsäure und Äthylzellulose enthält, und wenn das Medikament aus der aus Propranolol und Diltiazem bestehenden Gruppe gewählt ist, das Überzugsmembran eine Mischung aus Paraffin und Methacrylsäure-Kopolymer enthält.

10. Verfahren nach Patentanspruch 9, **dadurch gekennzeichnet,** dass das Überzugsmembran durch eine Lösung aufgebracht wird, welche beide Komponenten wie Stearinsäure/Äthylzellulose oder Paraffin/Methacrylsäure-Kopolymer enthält.

11. Verfahren nach Patentanspruch 9, **dadurch gekennzeichnet,** dass das Überzugsmembran in wechselweisen und getrennten Schichten aufgebracht wird, während es sich in einem geschmolzenen Zustand befindet.

Revendications

1. Composition pharmaceutique orale à effet retard comprenant une multiplicité de petits pellets composés de microgranules de matière inerte; une couche de médicament appliquée sur ceux-ci et une membrane d'enrobage appliquée sur la couche de médicament, ladite membrane d'enrobage étant un mélange d'acide stéarique et d'éthyl-cellulose ou de paraffine et de copolymeres de l'acide méthacrylique, caractérisée en ce que le médicament est choisi parmi le groupe comprenant kétoprofen, paracétamol, propranolol, diltiazem, isosorbide-5-mononitrate, phénylepropanolamine et diacerheyn, où, quand le médicament est choisi parmi le groupe comprenant kétoprofen, paracétamol, phénylepropanolamine, isosorbide-5-mononitrate et diacerheyn, la membrane d'enrobage se compose d'un mélange d'acide stéarique et d'éthyl-cellulose, et quand le médicament est choise parmi le groupe comprenant propranolol et diltiazem, la membrane d'enrobage se compose d'un mélange de paraffine et de copolymères de l'acide méthacrylique, et en ce que l'effet retard obtenu par le médicament "in vitro" est de 4 à 22 heures ou plus.

2. Composition pharmaceutique selon la revendication 1, caractérisée en ce que le médicament est kétoprofen et la membrane d'enrobage se compose de 4,16% en poids d'acide stéarique et 2,48% en poids d'éthyl-cellulose, basés sur la masse du médicament.

3. Composition pharmaceutique selon la revendication 1, caractérisée en ce que le médicament est paracétamol et la membrane d'enrobage se compose de 15,12% en poids d'acide stéarique et 3,05% en poids d'éthyl-cellulose, basés sur la masse du médicament.

4. Composition pharmaceutique selon la revendication 1, caractérisé en ce que le médicament est isosorbide-5-mononitrate et la membrane d'enrobage se compose de 2,84%, en poids d'acide stéari-

que et 26,3%, en poids d'éthyl-cellulose, basés sur la masse du médicament.

5. Composition pharmaceutique selon la revendication 1, caractérisée en ce que le médicament est phénylpropanolamine et la membrane d'enrobage se compose de 2,43% en poids d'acide stéarique et 24,3% en poids d'ethyl-cellulose, basés sur la masse du médicament.

6. Composition pharmaceutique selon la revendication 1, caractérisée en ce que le médicament est diacerheyn et la membrane d'enrobage se compose d'1,25% en poids d'acide stéarique et de 5,5% en poids d'éthyl-cellulose, basés sur la masse du médicament.

7. Composition pharmaceutique selon la revendication 1, caractérisée en ce que le médicament est propranolol et la membrane d'enrobage se compose de 16,36% en poids de paraffine et 1,81% en poids de copolymere de l'acide méthacrylique, basés sur la masse du médicament.

8. Composition pharmaceutique selon la revendication 1, caractérisée en ce que le médicament est diltiazem et la membrane d'enrobage se compose de 29,8% en poids de paraffine et 6,65% en poids de copolymère de l'acide méthacrylique, basés sur la masse du médicament.

9. Procédé pour la préparation d'une composition pharmaceutique orale à effet retard suivant la revendication 1, comprenant l'enrobage de microgranules de matière inerte d'une couche de médicament et la subséquente application d'une membrane d'enrobage sur ladite couche de médicament, caractérisé en ce que le médicament est choisi parmi le groupe comprenant kétoprofen, paracétamol, propranolol, diltiazem, isosorbide-5-mononitrate, phénylepropanolamine et diacerheyn, et la membrane d'enrobage est un mélange d'acide stéarique et d'éthyl-cellulose ou de paraffine et de copolymères de l'acide méthacrylique, où, quand le médicament est choisi parmi le groupe comprenant kétoprofen, paracétamol, phénylepropanolamine, isosorbide-5-mononitrate et diacerheyn, la membrane d'enrobage se compose d'un mélange d'acide stéarique et d'éthyl-cellulose, et quand le médicament est choise parmi le groupe comprenant propranolol et diltiazem, la membrane d'enrobage se compose d'un mélange de paraffine et de copolymères de l'acide méthacrylique.

10. Procédé selon la revendication 9, caractérisé en ce que la membrane d'enrobage est appliquée sous forme d'une solution contenant ou les composants acide stéarique/éthyl-cellulose ou les composants paraffine/copolymères de l'acide méthacrylique.

11. Procédé selon la revendication 9, caractérisé en ce que la membrane d'enrobage est appliquée sous forme de couches alternées et séparées à l'état fondu.

FIG 1

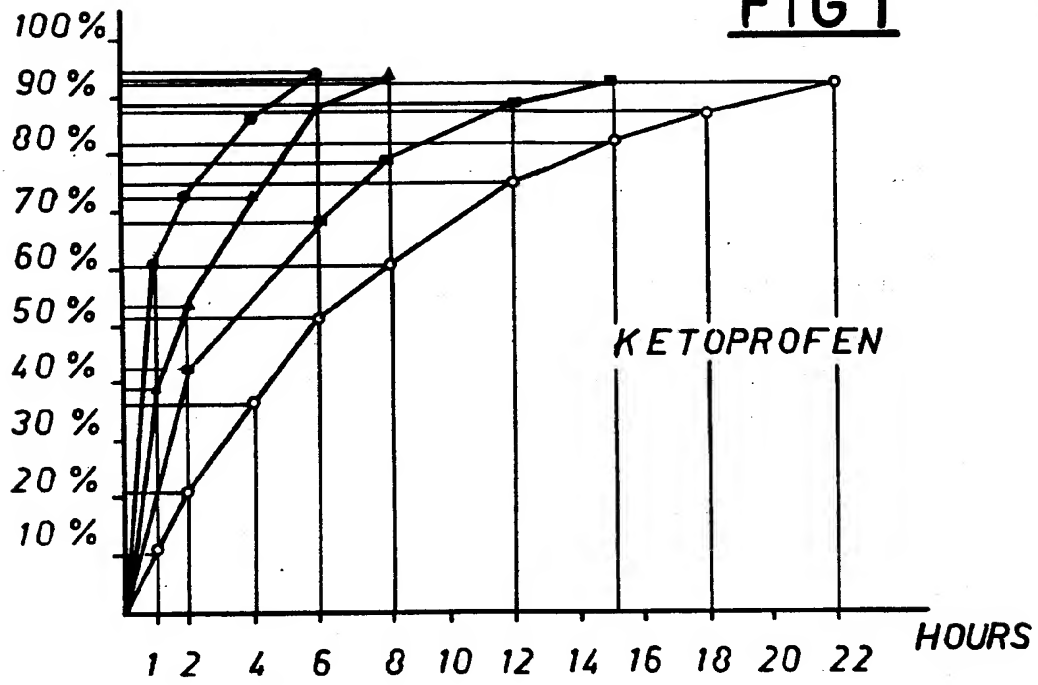
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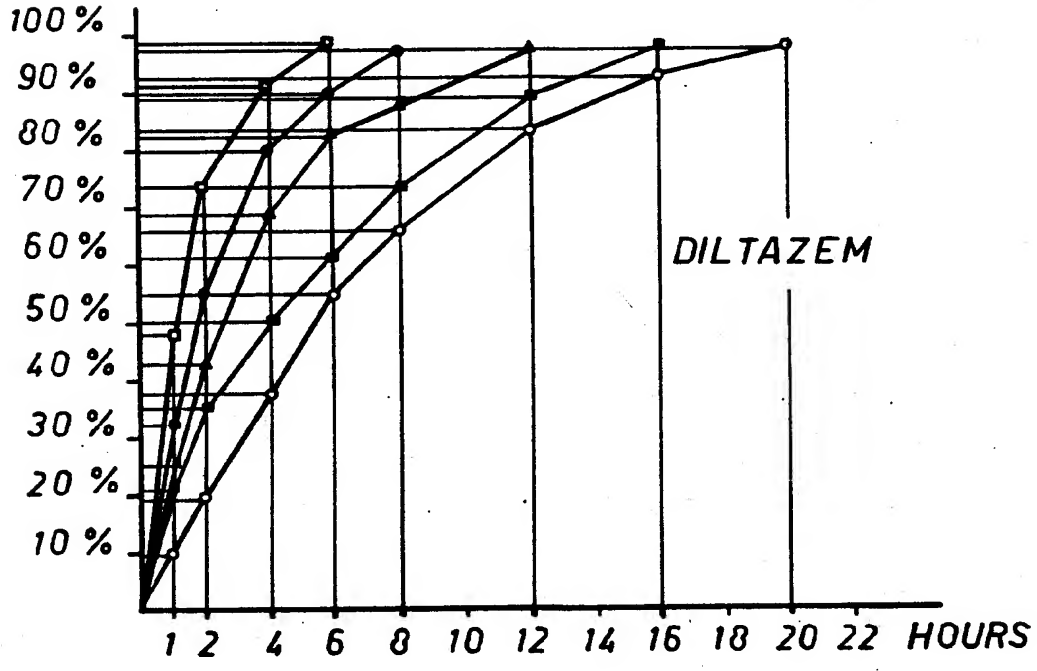
FIG 2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